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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,036	09/30/2002	Paul R. Sanberg	1372.623.PRCWOUS	5509

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EXAMINER	
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ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/009,036	SANBERG ET AL.	
	Examiner	Art Unit	
	DANIEL KOLKER	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/23/08, 5/27/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,7,10,12-17 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2,4,7,10,12-17,19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The remarks, amendments, and declarations filed 23 May 2008 and 27 May 2008 have been entered. Claims 1 - 2, 4, 7, 10, 12 - 17, and 19 are pending and under examination.

Withdrawn Rejections and Objections

2. The rejection under 35 USC 112, second paragraph is withdrawn in light of the amendments which clarify the scope of the claims.

Maintained Rejections

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 – 2, 4, and 17 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Weiss (U.S. Patent 5,851,832) in view of Sanberg (1997. Soc. Neurosci Abstr 23(1-2):346, abstract 140.9) and Grabowski (1994. Exp Neurol. 127(1):126-136).

This rejection stands for the reasons previously made of record and explained in further detail below. The reasons why the limitations of each claim have been met or suggested by the prior art references have been set forth in the previous office actions and for the sake of brevity will not be repeated here. Rather applicant is referred to the previous office actions for a detailed explanation. Applicant did not argue that the prior art references fail to teach or suggest any limitations recited in the claims, with the exception of administration “to a plurality of

brain areas", recited in each of the independent claims. Rather applicant argued that at the time the invention was made, the state of the art was such that treatments shown to be effective for treating stroke in animal models had not been shown to be effective in humans. As administration to humans is explicitly claimed, applicant argues that the prior art references cited by the examiner, which detail prophetic treatment of humans but fail to show actual reduction to practice of such treatment, cannot be considered enabling for these claims. Furthermore, applicant argues that there is not a correlation between treatment of stroke in animal models and treatment in humans, so there would not have been a reasonable expectation of success in extending the treatments to humans as claimed.

Applicant's arguments have been fully considered but they are not persuasive. The crux of the argument is that rodent models of ischemia were entirely useless in their ability to predict human therapies. The examiner has closely reviewed the arguments and accompanying declaration, and has found that they are not persuasive. At the time the invention was made, rodent models of stroke, including cerebral artery occlusion, were standard in investigating possible therapies in humans. See for example Zhang 1997 (Brain Research 766:83 – 92), who describes a new and improved model of cerebral ischemia in rats. Zhang teaches that the model is more reproducible than previous models (p. 83 second column) and produces changes in neurological function, cerebral blood flow, as well as changes visible at the microscopic level, each of which are similar to the changes seen in human stroke (see results and discussion sections of the paper). Additionally, Zhang predicts that the model will be useful in finding new treatments for stroke (p. 91 final paragraph). While Zhang does not explicitly indicate which therapies are in fact effective in treating human stroke, the reference provides detailed instructions to one of ordinary skill in the art as to how to generate the animal models of stroke described in the references cited above, and indicates that the model is expected to be useful in identifying new therapies.

Applicant states, at p. 6 of the remarks filed 25 May 2005, that "animal results were NOT translated to humans at the time of the filing of the patent application and even later" (emphasis in original). At the time the invention was made, several therapies for human stroke were known. These included urokinase and heparin, among others; this is not to be construed as an exhaustive list. These specific drugs had also been shown to be effective in treating rodent models of ischemic stroke.

While rodent cerebral artery occlusion studies may well reveal false positives (therapies which are efficacious in rodents but not in humans), and may fail to reproduce every single aspect of stroke in humans, the models nonetheless are reasonable. Therapies known to be effective for treatment of stroke in humans are also effective for treatment of stroke in rodents. For example Gonner 1998 (Stroke 29(9):1894 - 1900) teaches that urokinase is effective in ameliorating stroke in humans when given up to four hours (i.e., more than three hours as recited in claim1) after the stroke (p. 1896 second column second paragraph). According to Gonner, such treatment improves neurological outcome. Additionally, Gonner indicates that urokinase treatment can be used later relative to stroke onset than tPA (p. 1899 second paragraph). Takano 1998 (Neurology 50:870-875) teaches that prourokinase, which is converted to urokinase, improves outcome after experimentally-induced stroke in rats. Additionally Kay 1995 (The New England Journal of Medicine 333:1588 – 1593) teaches that low-molecular-weight heparin given within 48 hours of stroke significantly improves outcome up to six months later. Li 1998 (Brain Research 801:220-223) teaches that low-molecular weight heparin improves clinical outcome in rats with experimentally-induced stroke. Furthermore the reference by Bonn 1998 (The Lancet 352:119, cited as reference 24 on IDS filed 15 November 2002) indicates that rodent models of stroke are a reasonable preclinical model for transplantation of cells into humans.

In the remarks and declaration filed 25 May 2008, applicant makes several additional points, each of which will be addressed below. Applicant states (remarks, p. 5, end of second paragraph, and p. 6 first complete paragraph) that administration of at least 6 million cells was more effective than administration of 2 million cells, and that this was surprising. It is not immediately apparent what is surprising about increased efficacy of a larger dose (6 million cells being three times as many as 2 million cells). Applicant also states (p. 5, end of third paragraph) that the specification "as filed shows a clear benefit in the use of at least six million viable cells." The examiner has no doubt that the specification shows such a benefit, and notes there is not an enablement rejection of record. The claims appear to be enabled over their scope.

Applicant also argues, on p. 7 final paragraph of the remarks and in Dr. Weschler's declaration that selection of multiple sites for administration of a treatment post-stroke not only would have been non-obvious, but also would have been deleterious. The examiner contends that it was well-known in the art to administer stroke treatments at multiple locations within the

brain at the time the invention was made in order to ensure that multiple affected brain areas receive treatment. See for example Weiss '832 patent column 42 lines 50 – 56, which indicate that the treatments are to be administered to multiple sites. Additionally, the examiner notes that Wang 1997 (Journal of Neuroscience 17(11):4341 – 4348) teaches administration of a therapeutic treatment (GDNF) to multiple sites within the cortex (see p. 4342, paragraph spanning the two columns), providing evidence that administration to multiple sites was well-known/

Additionally, Dr. Weschler stated that selection of the doses recited in the claims would not have been obvious to one of ordinary skill in the art (declaration paragraph 9). The examiner had previously contended that by scaling up the results set forth the Sanberg reference, one of ordinary skill in the art would have found it obvious to administer 10 million cells. Applicant argues (remarks, paragraph spanning pp. 7 – 8) and the declarant states (declaration, paragraph 9), that the dose used in the specification was not obvious. First, it is noted that optimization of doses and concentrations are generally not supportive of patentability (MPEP § 2144,05 (II)). Additionally, it appears that applicant is arguing limitation which are not present in the claims. The examiner had contended that administration of 10 million cells, which is "at least 6 million" cells, as claimed, would have been obvious. No claim recites a maximum number of cells to be administered, or is limited to administration of exactly 6 million cells.

The declarations under 37 CFR 1.132 filed 23 May 2008 and 27 May 2008 (it appears the same declaration was submitted twice; note that text appears identical between the two, and both are dated by the declarant on 12 May 2008) are insufficient to overcome the rejections of record based upon obviousness as set forth in the last Office action for the following reasons.

At paragraph 2, the declarant quotes articles which suggest failure of animal models of stroke to successfully identify therapies for stroke. As set forth in the paragraphs above, several treatments for stroke are known, and have been shown to be effective in both humans and rodent models of stroke. See pages 3 - 4 of this office action. This indicates that rodent models of stroke are useful in identifying treatments for stroke in humans. See also Chopp et al. (U.S. Patent 6,245,757, issued 12 June 2001, filed 1 October 1998). Chopp teaches administration of progestin is therapeutic for stroke in rodents (see for example column 11). The reference also claims treatment of ischemia (claim 1) by administering progestin after ischemia and specifically includes claims drawn to treatment of stroke in humans (see claims 3 - 4). This reference suggests that even before the instant patent application was filed, animal data from cerebral

artery occlusion studies were supportive of therapeutic treatment of human stroke. At paragraph 3, the declarant states that treatment of stroke has a long-felt need. While there are in fact many patients each year who suffer from stroke, such a statement is insufficient on its own to overcome the examiner's determination of obviousness. Treatments for human stroke were known (including but not limited to low-molecular weight heparin and urokinase), animal models of stroke identified these same treatments as effective. Since the prior art of record indicates the predictive value of the animal studies, it would have been obvious to one of ordinary skill in the art to treat humans as claimed, given that the references by Weiss and Sanberg show reduction to practice of treatment in rodents and guidance as to treatment of stroke in humans. At paragraph 5, the declarant states that "preclinical studies in rodents had NO POSITIVE PREDICTABILITY in humans" (emphasis in original). This has been refuted by the examiner as set forth above.

At paragraph 6, the declarant states "The inventors of the instant patent were the first to achieve successful stroke treatment in humans." This statement is not supported by the evidence of record. See for example Gonner 1998 and Kay 1995, cited above, each of which show treatment of stroke in humans. Even if the instant inventors had been the first to treat stroke in humans, that would not speak to the non-obvious nature of the invention claimed. A claimed method can be novel but still be obvious. The examiner concedes that the evidence of record indicates that the instant applicants were the first to administer "at least six million viable hNT neuronal cells to a plurality of brain sites involved in" stroke to a human patient as recited in claim 1. There is no rejection under 35 USC 102 in this case. However, even though the claimed method may be novel, it nonetheless would have been obvious.

At paragraph 8, the declarant speaks to the non-obvious nature of administration to multiple sites. As set forth on pp. 4 – 5 of this office action, administration to multiple sites for treatment of stroke was well-known at the time the invention was made, and is taught by Weiss. Additionally the declarant states that no patients showed inflammation. While this is obviously important for the sake of the patients' health, it does not overcome the examiner's determination of obviousness. The obvious nature of dosing (declaration, paragraph 9) is discussed above. The declarant states that 6 million cells used in the examples was not obvious. The examiner again notes that administration of exactly 6 million cells is not claimed, and furthermore the examiner has provided reasons why administration of "at least 6 million" cells as claimed would have been obvious.

For at least the reasons above, the rejection over Weiss in view of Sanberg and Grabowski is maintained.

4. Claims 7, 10, 12 – 17, and 19 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sanberg (1996. Soc. Neurosci. Abstr. 22(1-3):578, abstract 232.9) in view of Weiss (U.S. Patent 5,851,832) and Uchida (1995. Exp. Neurol 132:194-208).

This rejection stands for the reasons previously made of record. The reasons why the specific claim limitations are met by the cited references have been set forth previously; see office action mailed 23 November 2007, pp. 5 (final paragraph) – 7. For the sake of brevity, they will not be reiterated herein.

Applicant argues, on pp. 8 – 9 that the claimed invention would not have been obvious for several reasons. Applicant argues that there is no reasonable expectation of success in treatment of humans. This has been discussed at length above. Applicant argued that "sterility is certainly not a given if one wants to maximize the yield of viable cells. Just using a sterile solution control and sterile collection apparatus are insufficient to assure sterility of the cellular composition" (paragraph spanning pp. 8 – 9). As set forth previously, the Weiss '832 patent teaches sterile technique to be used in manipulating cells. It is within the skill of the artisan to use sterile technique to maintain the sterility of the composition. Note that the claims which recite administration of sterile compositions do not recite any additional steps beyond administration, no steps as to how to make the compositions sterile are recited. The word "sterile" refers to a property that appears to be provided by the prior art references themselves. Inclusion of the claims in this rejection is proper even though the references might be silent as to whether the compositions actually are sterile; see MPEP § 2112.

Applicant also argues that the examiner had contended that Weiss suggests administration of 38 million cells to a person, not 6 million as claimed. This argument is not persuasive. The claims do not recite a maximum number of cells to be administered. The claims are drawn to administration of at least 6 million cells. The 38 million cells suggested by Weiss is at least 6 million cells. Therefore this argument that the invention is non-obvious is not persuasive, as the claimed invention encompasses administration of 38 million cells.

Finally, applicant argues that Uchida is equivocal as to whether the cells migrate, as recited in claim 15. The examiner agrees that the reference is not definitive. However, claim 15 does not recite any additional steps to make the cells migrate, and does not require that any

particular location be selected for administration. The claim only requires that the cells be administered "into a plurality of locations from which the hNT neuronal cells migrate to the damaged area." As set forth previously, Uchida teaches administration to the ventricles, which themselves of course are not the damaged tissue but are within the scope of regions from which cells migrate to the damaged area (see Uchida p. 198 first complete paragraph). The reference gives guidance as to administration to a region from which cells will migrate as claimed.

For the reasons set forth above, the rejection stands.

Conclusion

5. No claim is allowed.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANIEL KOLKER whose telephone number is (571)272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel E. Kolker, Ph.D./
Patent Examiner, Art Unit 1649
August 11, 2008